REMARKS

Claims 1-3, 11, 12, 15, and 16 are pending in this application. Claims 1, 2, 11, and 12 have been amended. No new matter has been added.

35 U.S.C. § 102

The Applicant respectfully submits that the three references cited by the Office Action as allegedly anticipating claims 1-3, 11, 12, 15, and 16 fail to teach all of the elements recited in these claims. For example, none of the cited references describe:

(i) a plurality of first and second polynucleotides encoding a Fab library, the library comprising a plurality of vectors wherein each vector contains a first and second cloning region wherein each cloning region comprises at least one vector unique restriction enzyme cleavage site; or a plurality of vectors wherein each vector of the plurality comprises a first and second cloning region wherein each cloning region comprises at least one vector unique restriction enzyme cleavage site; or

(ii) a plurality of first and second polynucleotides encoding a Fab library, the library comprising a plurality of vectors wherein each vector comprises first and second cloning regions into which a member of a first plurality of polynucleotides and a member of a second plurality of polynucleotides, respectively, are cloned; or a plurality of vectors wherein each vector of the plurality comprises first and second cloning regions into which a member of a first plurality of polynucleotides and a member of a second plurality of polynucleotides, respectively, are cloned.

The Applicant respectfully requests that the rejection of the claims as allegedly anticipated be withdrawn.

U.S. Patent No. 5,969,108

The Office Action alleges that claims 1-3, 11, 12, 15, and 16 are anticipated by U.S. Patent No. 5,969,108 ("the '108 patent"). The Office Action at page 4 states:

> The claim (Claim 1) recites "a member of a first (or second) plurality of variable polynucleotides", which limits each one of the vector within the library to comprise only a single first member and a single second member derived from the pluralities of first and

> second members. The claim does not recite that the vectors comprise a first plurality of variable polynucleotides and further comprise a second plurality of variable polynucleotides, as applicant seems to argue.

The Applicant has amended claims 1 and 11 to recite "wherein the plurality of vectors comprises the first plurality of variable polynucleotides and the second plurality of variable polynucleotides." This amendment clarifies that the plurality of vectors comprises both the first and second pluralities of polynucleotides.

The Office Action next alleges at pages 4-5 that:

> Applicant mainly argues that the '108 patent does not teach every elements recited in the instant claims. Contrary to applicant's assertion, the cited reference ('108 patent) teaches individual vectors (i.e. each single vector) comprising "a member of a first plurality of variable polynucleotides" and "a member of a second plurality of variable polynucleotides". The '108 patent teaches a library of vectors comprising a combination of heavy and light chain variable regions (corresponding to a member of a first (or second) plurality of variable polypeptides) (see the Examples 1-48 of the reference). For example, in Example 22, the reference teaches the generation of a library of vectors with each vector comprising a heavy and a light chain variable regions. Each of the heavy and light chain variable regions is a member of a library (or a plurality) of variable regions (see col. 62-63).

The Applicant respectfully disagrees with this allegation and submits that the '108 patent fails to teach every element recited in the claims. Although the '108 patent describes vectors that contain a combination of heavy and light chain variable regions, the library vectors described in the '108 patent do not contain all of the elements recited in claim 1 or 11.

For instance, Example 22 of the '108 patent (starting at col. 62) describes a vector containing a fixed heavy chain variable region or a fixed light chain variable region. The example does not teach a plurality of vectors that comprises both a first plurality of polynucleotides and a second plurality of polynucleotides, as recited in the amended claims.

Further, the '108 patent (e.g., Example 22) fails to describe a vector wherein "each cloning region comprises at least one, for the vector unique, restriction enzyme cleavage site" as recited in the claims. Instead, the '108 patent teaches that "It would be useful to design vectors that enable the use of restriction enzymes that cut DNA infrequently" (col. 41, lines 62-63; emphasis added). Thus, a vector unique cleavage site is not taught by the '108 patent. Not only does the '108 patent fail to teach even one vector unique restriction site, it does not teach the

presence of at least two vector unique restriction enzyme cleavage sites, at least one in each cloning region, as recited in the claims.

Next, amended claims 1 and 11 recite that the member of the first plurality of polynucleotides is cloned into the first cloning region of the vector and the member of the second plurality of polynucleotides is cloned into the second cloning region. This amendment clearly indicates that the vector comprises two cloning regions. In contrast, all of the examples in the '108 patent that describe the preparation of libraries utilize only a single cloning site. For instance, as described in Example 14 of the '108 patent (starting at col. 49), the first and second polynucleotides are combined by PCR assembly to generate one fragment: "The separate amplified VH, VLK and linker sequences now have to be assembled into a continuous DNA molecule by use of an 'assembly' PCR" (col. 49, lines 38-40; emphasis added). The one continuous fragment is then inserted into a single site in a vector. Thus, the '108 patent fails to describe a plurality of vectors in which a first polynucleotide is cloned into a first cloning region and a second polynucleotide is cloned into a second cloning site of the vector, as required by the claims. In addition, the PCR assembly method does not result in at least two vector unique restriction enzyme cleavage sites.

The Office Action at pages 5 next alleges that:

> Applicant argues that the '108 patent's teaching of the "fourth approach" of generating libraries of antibodies (col. 7, line 5+) does not anticipate the claimed invention, because the "fourth approach" teaches that one of the heavy and light chains "is kept fixed" (col. 7, line 9+). This is not found persuasive, because in the "fourth approach" taught by the '108 patent, either the heavy or the light variable regions (reads on the first and second variable polypeptides) are derived from a library of heavy variable regions or a library of light variable regions (see Examples 22 and 46). For example, Example 22 uses antibody heavy chain variable regions and light chain variable regions derived from repertoires (i.e. libraries or pluralities) of heavy and light chain variable regions. Thus, each of the heavy chain and light chain variable is a member of a first (or second) plurality of variable polypeptides.

Again, the Applicant respectfully disagrees. The shortcomings of Example 22 are discussed above. Example 46 of the '108 patent (starting at col. 104) also fails to describe all of the elements recited in the claims. In Example 46, a fixed heavy chain variable region is used. In contrast, the amended claims recite a plurality of vectors that comprises both a first plurality of polynucleotides and a second plurality of polynucleotides. In addition, Example 46 fails to

describe a vector wherein "each cloning region comprises at least one, for the vector unique, restriction enzyme cleavage site" as recited in the claims. Finally, to prepare a vector that contains a heavy chain variable region and a light chain variable region, Example 46 uses the method of Example 14, i.e., PCR assembly was used to prepare a single fragment that was inserted into a single cloning site in a vector. As such, Example 46 fails to describe a plurality of vectors in which a first polynucleotide is cloned into a first cloning region and a second polynucleotide is cloned into a second cloning site of the vector.

The Office Action alleges at page 6 that:

> The reference ('108 patent) does specifically teach a library of vectors comprising both various heavy chain variable regions (a first plurality) and various light chain variable regions (a second plurality). For example, the reference teaches a vector comprising at least two cloning sites comprising restriction sites, ribosome binding site (RBS), and the antibody variable regions (reading a the first and second plurality) (see Figure 45). Although Figure 45 depicts a vector with one particular heavy and one particular light chain variable region, such a vector can be used to generate a library of vectors that comprises different heavy and light chain variable regions. Indeed, the reference teaches the generation of such a library of vectors in detail (see Examples 26 and 39). For example, Example 39 teaches the following (see col. 88, lines 44+):
>
> > "This example shows that functional Fv fragments can be expressed on the surface of bacteriophage by non-covalent association of VH and VL domains. The VH domain is expressed as a gene III fusion and the VL domain as a soluble polypeptide. Thus Fv fragments can be used for all the strategies discussed for Fab fragments including dual combinatorial libraries (example 26)."
>
> In other words, the reference teaches the vector depicted in Figure 45 (corresponding to Example 39) can be used to express both the variable heavy chain domains (the first plurality) and variable light chain domains (the second plurality) to form library of antibody fragments via non-covalent association. Specifically, the reference teaches the vector depicted in Figure 45 can be used to generate dual combinatorial libraries (see col. 88, lines 48+), i.e. a vector library comprising two pluralities of variable regions.

The Applicant respectfully disagrees with this allegation. Figure 45 of the '108 patent "shows a map of the insert of sequences encoding FvD1.3 present in fd-tet FvD1.3 (example 39)" (col. 29, lines 28-29; emphasis added). It does not depict a vector that comprises two cloning regions into which two polynucleotides are cloned. Rather, the figure shows an insert that contains two polynucleotides, and this one insert can be inserted into one cloning region of a vector. Further, neither Figure 45 nor Example 39 (starting at col. 88 of the '108 patent) describes a plurality of first and second polynucleotides encoding a Fab library, the library comprising a plurality of vectors wherein each vector contains a first and second cloning region wherein each cloning region comprises at least one vector unique restriction enzyme cleavage

site; or a plurality of vectors wherein each vector of the plurality comprises a first and second cloning region wherein each cloning region comprises at least one vector unique restriction enzyme cleavage site. Nor do they describe a plurality of polynucleotides encoding a Fab library, the library comprising a plurality of vectors wherein each vector comprises a first and second cloning region into which a member of a first plurality of polynucleotides and a member of a second plurality of polynucleotides, respectively, are cloned; or a plurality of vectors wherein each vector of the plurality comprises first and second cloning regions into which a member of a first plurality of polynucleotides and a member of a second plurality of polynucleotides, respectively, are cloned.

In addition, Example 39 only describes the introduction of one specific heavy chain variable region and one specific light chain variable region. Example 39 does not describe a plurality of vectors wherein each vector comprises two cloning regions where each of the two cloning regions of the vector comprises at least one, for the vector unique, restriction enzyme cleavage site, as recited in the claims. Finally, to generate the vector containing the specific heavy chain variable region and specific light chain variable region, a single insert containing VH and VK regions was isolated from one vector and inserted into a single cloning site in another vector:

> The vector fd-DOG1 was digested with the restriction enzymes PstI and Xho1. From the Fv expression plasmid pSW1-VHD1.3-VKD1.3myc version 3/pUC119 (Ward et al., 1989 supra) a Pst 1/Xho I-digested restriction fragment was isolated that carries the VH domain coding sequence (terminated by 2 stop codons), a spacer region between VH and VK genes including a ribosome-binding site for expression of the VK gene, a pelB leader sequence, and, following in frame, the VK gene. This fragment was cloned into the digested fd-DOG vector to generate the construct fd-tet Fv D1.3. (the '108 patent, col. 88, line 62 to col. 89, line 5; emphasis added)

Thus, this example also fails to describe a plurality of vectors wherein the plurality of vectors comprises first and second pluralities of polynucleotides.

With respect to Example 26 of the '108 patent, the Office Action further alleges at page 7:

> Example 26 (as alluded to in Example 39) of the reference provides additional teachings of generating a library of vectors that encode different heavy and light chain variable regions. Specifically, Example 26 recites the heavy and light chains of antibody fragments can be encoded together in the same vector or in different vectors (see col. 68, lines 22+). Furthermore, Example 26 teaches the generation of antibody libraries with

> different heavy and light chain variable regions with both the heavy and light chains encoded by the same vector (see bridging para, of Cols. 68 and 69). In addition, Example 26 teaches that the libraries of heavy and light chains (reads on the first and second pluralities) can be expressed from the same vector using different promoters as separate transcripts (see col. 69, lines 7+), hence separate translations that require separate ribosome binding sites on the same vector.

The description provided in Example 26 of the '108 patent (starting at column 68) also fails to disclose all of the elements recited in the claims. Example 26 fails to describe a plurality of vectors wherein each vector comprises two cloning regions in which each cloning region comprises at least one, for the vector unique, restriction enzyme cleavage site, as recited in the claims. Finally, as described in Example 26, to prepare a library, PCR assembly was used to prepare one fragment containing the heavy and light chains, and the one fragment was then ligated into a single cloning site in a vector:

> Also demonstrated here is that heavy and light chains encoded on the same vector (construct II), or on different vectors (constructs III and IV) can be displayed as Fab fragments. This offers two distinct ways of making random combinatorial libraries for display. Libraries of heavy and light chain genes, amplified by PCR, could be randomly linked by a 'PCR assembly' process (example 14) based on 'splicing by overlap extension', cloned into phage(mid) display vectors and expressed from the same promoter as part of the same transcript (construct II) as above, or indeed from different promoters as separate transcripts. (col. 68, line 65 to col. 69, line 8; emphasis added)

In contrast, the claims recite that the member of a first plurality of polynucleotides and the member of a second plurality of polynucleotides are cloned into two cloning regions of the vector. Thus, Example 26 also fails to describe this element of the claims.

For at least these reasons, the Applicant respectfully submits that claims 1-3, 11, 12, 15, and 16 are not anticipated by the '108 patent and requests that this rejection be withdrawn.

EP Patent No. 844306 A1

The Office Action alleges that claims 1-3, 11, 12, 15, and 16 are anticipated by EP 844306 A1 ("the '306 application"). The grounds for rejection re-iterate those presented with respect to the '108 patent, discussed above. Thus, for the reasons presented above in addressing the rejection based on the '108 patent, the Applicant respectfully disagrees with the rejection and requests that the rejection of claims 1-3, 11, 12, 15, and 16 as allegedly anticipated by the '306 application be withdrawn.

U.S. Patent No. 6,172,197

The Office Action next alleges that claims 1-3, 11, 12, 15, and 16 are anticipated by U.S. Patent No. 6,172,197 ("the '197 patent"). The rejection is based on the same allegations as those given for the rejection based on the '108 patent. Thus, the Applicants respectfully disagrees and requests that the rejection of claims 1-3, 11, 12, 15, and 16 as allegedly anticipated by the '197 patent be withdrawn.

35 U.S.C. § 103

The Office Action has rejected claims 1-3, 11, 12, 15, and 16 as allegedly obvious in light of either the '108 patent or the '197 patent. The Applicant respectfully disagrees and submits that a *prima facie* case of obviousness has not been established by the Office Action. For example:

(i) no reasonable expectation of success has been articulated by the Office Action (MPEP § 2143);

(ii) the proposed modification would render the prior art unsatisfactory for its intended use (MPEP § 2143.01(V)); and

(iii) the proposed modification would change the principle of operation of the cited references (MPEP § 2143.01(VI)).

No reasonable expectation of success has been articulated by the Office Action

To establish a *prima facie* case of obviousness, the Office Action must establish a motivation to modify the prior art reference, a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations (MPEP § 2143).

The Applicant does not believe that the motivation articulated in the Office Action or the purported teachings of claim elements alleged by the Office Action have merit. However, the Applicant further submits that the Office has not even articulated a reasonable expectation of success in modifying either prior art reference. Thus, the Applicant respectfully requests that the obviousness rejection of claims 1-3, 11, 12, 15, and 16 be withdrawn because no *prima facie* case of obviousness has been established.

The proposed modification would render the prior art unsatisfactory for its intended use

The Applicant respectfully submits that modifying the '108 patent or the '197 patent to arrive at the subject matter recited in the claims would render the patent inoperable for its intended purpose (MPEP § 2143.01(V)).

As discussed above, to prepare phage display libraries, the '108 patent uses a PCR assembly technique (see, e.g., Example 14 starting at col. 49 of the '108 patent). Briefly, as described in the '108 patent, the PCR assembly technique involves separately amplifying heavy chain variable regions and light chain variable regions. The variable regions are then "assembled into a continuous DNA molecule" (col. 49, lines 38-40), i.e., one fragment is formed. The one fragment contains both the heavy and light chain variable regions. The one fragment is then digested with restriction enzymes and ligated into a single cloning region in a vector that was digested with the same enzymes (col. 54, lines 26-34). The PCR assembly method is utilized in all of the library-preparation protocols described in the '108 patent.

In summary, to prepare libraries, the '108 patent only describes using the PCR assembly method, which generates one fragment containing two coding regions, and inserting the one fragment into one cloning region. The same method is described in the '197 patent. In contrast, the vectors recited in claims 1 and 11 contain *two* cloning regions and *two* polynucleotides are cloned into these two regions.

As stated in MPEP § 2143.01(V), "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). The Applicant submits that if the PCR assembly method of the '108 patent (or the '197 patent) was modified so that two fragments were prepared, that method would be unsatisfactory for cloning into a single cloning region in a vector, the only cloning method taught or suggested by the '108 patent (or the '197 patent) for the construction of libraries. As a result, there is no suggestion or motivation to make the proposed modification. For at least this reason, the Applicant respectfully requests that the obviousness rejection of claims 1-3, 11, 12, 15, and 16 be withdrawn.

The proposed modification would change the principle of operation of the cited references

The Applicant respectfully submits that modifying the '108 patent or the '197 patent to arrive at the subject matter recited in the claims would change the principle of operation of those references (MPEP § 2143.01(VI)).

As discussed above, the '108 and '197 patents prepare phage display libraries by utilizing the PCR assembly method, which generates one fragment that is cloned into one cloning region in a vector. In contrast, the claims recite first and second polynucleotides cloned into first and second cloning regions in a vector.

As stated in MPEP § 2143.01(VI), the teachings of the references are not sufficient to render the claims *prima facie* obvious if the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). The Applicant submits that re-designing the PCR assembly method of the '108 and '197 patents to arrive at the subject matter recited in the claims would require a substantial reconstruction and redesign of this method. Indeed, the PCR method would need to be re-designed to generate two fragments containing polynucleotides instead of one fragment, and the vector used in the '108 and '197 patents for library preparation would need to be re-designed to create two cloning regions instead of one region. As the '108 and '197 patents only teach cloning one fragment into one cloning region to prepare libraries, changing this method to create two fragments for cloning into two cloning regions would change the basic principle under which the PCR assembly method was designed to operate. Thus, the teachings of the '108 patent or the '197 patent are not sufficient to render the claims *prima facie* obvious. For at least this reason, the Applicant respectfully requests that the obviousness rejection of claims 1-3, 11, 12, 15, and 16 be withdrawn.

CONCLUSION

The Applicant respectfully submits that all claims are in condition for allowance, which action is expeditiously requested. The Applicant does not concede any positions of the Examiner that are not expressly addressed above.

Enclosed is a $510 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10280-139001.

Respectfully submitted,

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